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Prognostic value of pretreatment inflammatory biomarkers in primary small cell carcinoma of the esophagus

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Abstract

Background: Growing evidence indicates that several inflammatory biomarkers may predict survival in patients with malignant tumors. The aim of this study was to evaluate the prognostic value of pretreatment biomarkers in patients with primary small-cell carcinoma of the esophagus (PSCCE).

Methods: A total of 73 PSCCE patients enrolled between January 2009 and December 2017 at the Affiliated Cancer Hospital of Zhengzhou University. The total lymphocyte counts (TLC), neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) prior to anticancer therapy were collected as inflammation biomarkers. The cutoff value was determined by Receiver operating characteristic (ROC). The Kaplan-Meier method was utilized to analyze overall survival (OS). Cox proportional hazards regression was used to identify univariate and multivariate prognostic factors.

Results: Univariate analysis showed that high NLR group (hazard ratio [HR] = 1.685; 95% CI: 1.001–2.838; $P = 0.047$) and high PLR group (hazard ratio [HR] = 1.716; 95% CI: 1.039–2.834; $P = 0.033$) were associated with poor OS, and TLC was not correlated with OS. On multivariate analysis, high PLR (hazard ratio [HR] = 1.751; 95% CI: 1.042–2.945; $P = 0.035$) was an independent prognostic factor of unfavorable OS.

Conclusions: Pretreatment PLR and NLR are correlated with OS. These biomarkers are easily accessible, cost effective, and can serve as a marker to identify high-risk patients for further designing personalized treatment and predicting treatment outcomes.

Introduction

Esophageal carcinoma is the sixth leading cause of cancer-related deaths worldwide and the third most common cancer in China.[1,2] The common types of esophageal cancer are squamous cell carcinoma and adenocarcinoma and primary small cell carcinoma of the esophagus (PSCCE) which is a relatively rare histological subtype, accounting for only 0.5–2.8% of all esophageal malignant tumors.[3] PSCCE is characterized by high aggression, early dissemination and poor prognosis.[4–9] Although the first case was noticed by McKeown in 1952, the lower incidence of PSCCE made it is difficult to establish a standard treatment.[10] Currently, different treatments including surgery, chemotherapy and radiotherapy have been performed alone or in combined strategies, but the outcomes are inconsistent.[6,7] Therefore, it is critical to identify reliable biomarkers for predicting prognosis and distinguishing patients with negative prognoses. Taking into account individual variability, using the prognostic biomarker to select eligible patients and administration of specific treatments is a promising strategy in the era of precision medicine.

Previous studies have shown that systemic inflammatory response plays an important role in tumorigenesis, development, and metastasis.[11,12] In the tumor microenvironment, inflammatory cells involved in angiogenesis, viability, mobility, and invasion.[13,14] Numerous evidence demonstrates that inflammatory biomarkers are correlated with the survivals of distinct types of cancers such as nasopharyngeal carcinoma,[15]

liver cancer,[16] cervical cancer,[17] lung cancer,[18] and esophageal cancer.[16,19] Patients outcomes can be effectively evaluated with pretreatment hematological biomarkers, including total lymphocyte count (TLC), neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR). In addition, the neutrophil, lymphocyte and platelet counts are easily available from the complete blood cell (CBC) counts in daily clinical practice and the cost of CBC is inexpensive. Nevertheless, there is little evidence of the relationship between these factors and the prognosis of PSCCE.

For the above reasons, we investigated whether the markers (TLC, NLR and PLR) have independent prognostic values in patients with PSCCE.

Methods

Patients

We performed a retrospective analysis on the hematologic and clinicopathological data of PSCCE patients from January 2009 to December 2017. The study was approved by the Ethical Board of the Affiliated Cancer Hospital of Zhengzhou University. Inclusion criteria were: (i) PSCCE proven by histopathology; (ii) blood samples prior to anticancer therapy were available; (iii) complete medical records. Exclusion criteria included: (i) non-primary esophageal carcinoma; (ii) pathologically confirmed or combined with squamous cell carcinoma, adenocarcinoma and other neuroendocrine carcinoma; (iii) if patients had received any other treatment before blood samples were collected; (iv) incomplete medical records; and (v) any inflammatory infections.

A total of 73 patients were screened in the analysis, and pathological diagnosis was confirmed PSCCE via endoscopic biopsy. Detailed physical and laboratory examination were performed after patients were admitted to the hospital. The tumor stage was classified according to the sixth edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual. Informed consent was obtained from all individuals prior to treatment.

Data collection

Clinical date including patient characteristics, laboratory outcomes, tumor location and stage, treatment, and pathological results were extracted from medical records. Blood samples were collected within 14 days prior to treatment in case the hematological parameters may have been influenced by antitumor treatments such as chemotherapy, radiotherapy, or nutritional support. The neutrophil, lymphocyte, and platelet counts were obtained from the pretreatment CBC. NLR was defined as the total neutrophil count divided by the total lymphocyte count. PLR was defined as the total platelet count divided by the total lymphocyte count. The optimal cutoff values of TLC, NLR, and PLR were calculated based on receiver operating curve. Patients were stratified according to the cutoff points. Other clinical characteristics were divided into different groups, including age (<60 or ≥60 years), gender (male or female), alcohol abuse (yes or no), tobacco abuse (yes or no), locations (upper, middle or lower), length of tumor lesion (≤6 or >6 cm), TNM stage (I, II, III, IV) and treatment modalities (surgery alone vs. chemoradiotherapy vs. surgery combined with chemoradiotherapy).

Statistical analysis

OS was served as the primary endpoint, and was calculated from the date of diagnosis by histopathology to the date of death from any cause, or the time of last follow-up. The connections between TLC, NLR, PLR and clinicopathological factors were analyzed by Chi-square test. The Kaplan-Meier method was used to conduct univariate analysis of survival. The variable with *P*-value less than 0.05 in univariate analysis were evaluated by multivariate logistic regression analysis. Cox proportional hazards regression was used to identify univariate and multivariate prognostic factors. All statistical analyses were conducted using SPSS version 22.0 (IBM Software Group, Chicago, USA). Differences were considered statistically significant at $P < 0.05$.

Results

Patient characteristics

The clinicopathological characteristics of PSCCE patients included in the study are illustrated in Table 1. There were 51 (69.9%) men and 22 (30.1%) women with a median age of 60 years, ranging from 37 to 77 years. The percentage of primary tumors located in the middle, upper and lower thoracic esophagus were 67.1% (n = 49), 2.7% (n = 2) and 30.1% (n = 22), respectively. The mean diameter of the tumor lesion was 5 cm (ranging from 1 to 11 cm). According to the sixth edition of the AJCC Cancer Staging Manual, six patients had stage I PSCCE (8.2%), 32 had stage II PSCCE (43.8%), 12 had stage III PSCCE (16.4%), and the remaining 23 patients had stage IV PSCCE (31.5%). Among the eligible individuals, 10 patients were treated by surgical resection (13.7%); 30 underwent surgery and chemoradiotherapy (41.1%); and 33 received chemoradiotherapy. The outcomes revealed that NLR and PLR were insignificantly associated with clinicopathological variables. In addition, significant correlations were observed between the TLC and alcohol and tobacco abuse, and there was no significant relationship between TLC and other features.

Table 1 Patient characteristics

	NLR			PLR			TLC		
Total (n = 73)	NLR ≤ 2.37 n = 44, 60.3%	NLR > 2.37 n = 29, 39.7%	*P*-value	PLR ≤ 136.5 n = 38, 52.1%	PLR > 136.5 n = 35, 47.9%	*P*-value	TLC ≤1.8 *109/L n = 43, 58.9%	TLC ≤1.8 *109/L n = 30, 41.1%	*P*-value
Age (years)									
<60	24	15	0.813	22	17	0.425	22	17	0.643
≥60	20	14		16	18		21	13	
Gender									
Male	31	20	0.892	29	22	0.211	28	23	0.29
Female	13	9		9	13		15	7	
Alcohol abuse									
Yes	10	12	0.089	12	10	0.78	9	13	0.04
No	34	17		26	25		34	17	
Tobacco abuse									
Yes	23	18	0.409	23	18	0.434	20	21	0.047
No	21	11		15	17		23	9	
Location									
Upper	1	1	0.458	0	2	0.206	2	0	0.128
Middle	32	17		27	22		31	18	
Lower	11	11		11	11		10	12	
Length (cm)									
≤6	30	17	0.404	28	19	0.084	27	20	0.734
>6	14	12		10	16		16	10	
TNM stage									
I	4	2	0.233	4	2	0.261	4	2	0.818
II	21	11		20	12		17	15	
III	4	8		5	7		8	4	
IV	15	8		9	14		14	9	
Treatment modalities									
S	5	5	0.756	6	4	0.083	6	4	0.557
S + CRT	19	11		19	11		16	14	
CRT	20	13		12	21		22	11	

NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; TLC, total lymphocyte count; S, surgery alone; S + CRT, surgery combined with chemoradiotherapy; CRT, chemoradiotherapy.

Survival analyses

The median follow-up time was 26.5 months, ranging from 1 to 116 months. At the end of follow-up, 69 patients died (94.5%). The median survival time was 22.0 months. The one-, three-, and five-year OS rates were 83.5%, 24.6%, and 6.8%, respectively. On univariate analysis, seven clinicopathologic features including tumor location, lesion length, TNM stage, treatment, pretreatment NLR and pretreatment PLR were found to be associated with OS (Table 2).

Relationships between inflammation biomarkers and OS

In the study, we determined cutoff points for TLC, NLR, and PLR to be 1.8, 2.37 and 145, respectively. According to the cutoff points,patients were divided into two separate groups (TLC ≥ 1.8 × 109 as high TLC group,TLC < 1.8 × 109 as low TLC group ; NLR ≥ 2.37 as high NLR group, NLR < 2.37 as low NLR group ; PLR ≥1 45 as high PLR group, PLR < 145 as low PLR group). Patients in the high NLR group had significantly poorer OS than those in the low NLR group (hazard ratio (HR) = 1.685; 95% CI: 1.001–2.838; P = 0.047, Fig 1). The patients in the high PLR group had significantly worse OS than those in the

Table 2 Univariate analysis of prognosis factors of overall survival

Variable	Hazard ratio	95% CI	*P*-value
Age (year)	1.105	0.682–1.789	0.685
Gender	1.081	0.639–1.826	0.772
Alcohol abuse	0.89	0.530–1.493	0.659
Tobacco abuse	1.134	0.701–1.835	0.609
Location	1.764	1.035–3.007	0.037
Length (cm)	1.672	1.004–2.785	0.048
AJCC	1.601	1.220–2.100	0.001
Treatment modalities	1.723	1.194–2.487	0.003
NLR	1.685	1.001–2.838	0.047
PLR	1.716	1.039–2.834	0.033
TLC	0.798	0.488–1.305	0.113

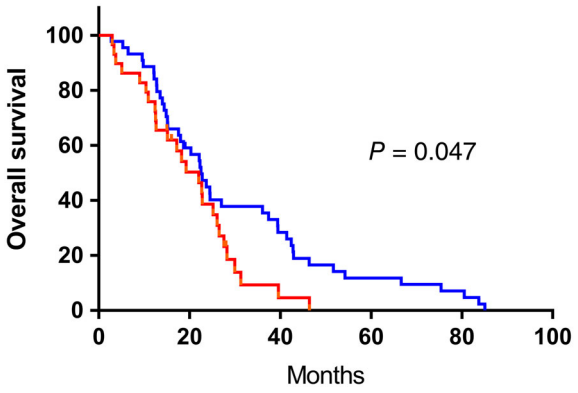

Figure 1 Kaplan-Meier analysis of NLR for overall survival in patents with PSCCE. (—) low NLR group, (—) high NLR group, (—) low NLR group-censored, and (—) high NLR group-censored.

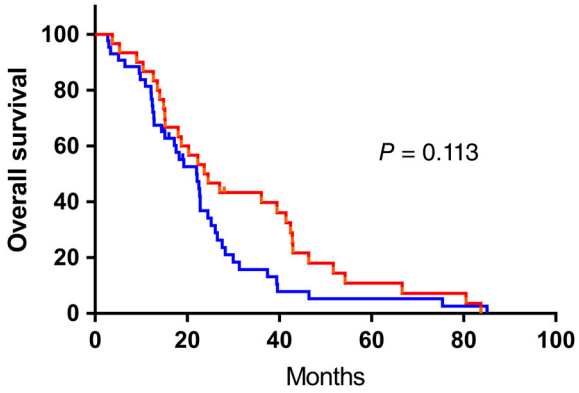

Figure 3 Kaplan-Meier analysis of TLC for overall survival in patents with PSCCE. (—) low TLC group, (—) high TLC group, (—) low TLC group-censored, and (—) high TLC group-censored.

low PLR group (hazard ratio (HR) = 1.716; 95% CI: 1.039–2.834; P = 0.033, Fig 2). Meanwhile, no statistical difference was observed in patients with different TLC (Fig 3). Furthermore, the multivariate analysis showed that low pretreatment PLR (hazard ratio (HR) = 1.751; 95% CI: 1.042–2.945; P = 0.035) was an independent predictor of superior survival in PSCCE. Treatment strategies (hazard ratio (HR) = 1.563; 95% CI: 1.081–2.262; P = 0.018) and tumor location (hazard ratio (HR) = 1.788; 95% CI: 1.037–3.083; P = 0.036) were significantly correlated with survival. There was no significant relationship between low pretreatment NLR and OS (Table 3).

Discussion

The present study demonstrated that pretreatment PLR is an independent prognostic factor for OS. Moreover, patients diagnosed as PSCCE with low PLR may have superior OS than those with the high PLR. NLR was also correlated with OS and TLC, NLR, as well as PLR were uncorrelated with other clinicopathologic factors. As far as we know, this is the first study to analysis the pretreatment TLC, NLR and PLR in the prediction of OS in patients with PSCCE.

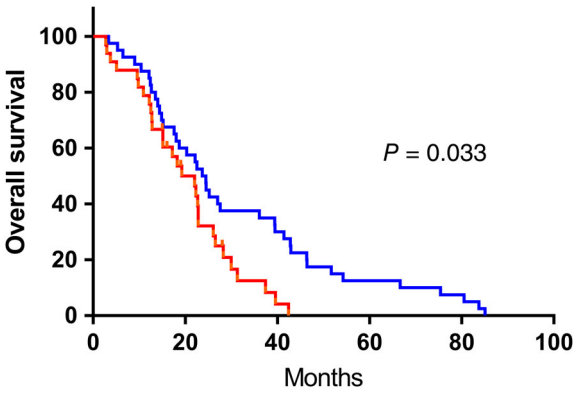

Figure 2 Kaplan-Meier analysis of PLR for overall survival in patents with PSCCE. (—) low PLR group, (—) high PLR group, (—) low PLR group-censored, and (—) high PLR group-censored.

Systemic inflammation involved in the process of tumorigenesis has been previously reported.[20] Chronic inflammation triggers molecular cascades in tumor cells, which promote tumor invasion and immune cell evasion.[21] The cancer-related inflammation recruiting T lymphocytes and activating chemokines, forming an immunosuppressive microenvironment, results in inhibited antitumor immunity which promotes tumor growth and metastasis.[20,22] Theoretically, after inflammatory cytokines have been released, the blood cells including neutrophils, lymphocytes, platelets and so on proliferate and instantly differentiate.[23] It is well known that neutrophils produce angiogenic cytokines and induce angiogenesis in tumor cells. Neutrophilia is frequently found in cancer patients and is associated with a poor prognosis.[24] In antitumor immune reactions, lymphocytes induce tumor cell apoptosis and suppress tumor cell proliferation and metastasis.[25] Platelets also contribute considerably to tumor growth, infiltration and dissemination.[26] The activation of platelets can lead to the release of angiogenic growth factors. Also, their adherence to tumor microvessels may enhance vascular permeability.[27] Many studies have reported that cancer

Table 3 Multivariate analysis for potential prognostic factors of overall survival

Variable	Hazard ratio	95% CI	*P*-value
Treatment modalities	1.563	1.081–2.261	0.018
PLR	1.751	1.042–2.945	0.035
Location	1.788	1.037–3.083	0.036
Length (cm)	1.604	0.935–2.750	0.086

produces interleukin-1, and interleukin-6, granulocyte colony-stimulating factor, as well as tumor necrosis factor-alpha, which may cause neutrophilia. Neutrophilia and thrombocytosis always symbolize a nonspecific response to the cancer-related inflammation.[22,28] Above all, systemic inflammatory biomarkers such as TLC, NLR, and PLR are expected to predict tumor prognosis. Systemic chemotherapy, radiotherapy or postoperative stress response will inevitably influence the CBC. Thus, this study assessed the potential prognostic value of TLC, NLR and PLR in patients with PSCCE who were newly diagnosed.

In previous studies, the utility of inflammation biomarkers as a prognostic factor was investigated in various types of solid tumors. Chen *et al.* demonstrated high NLR was an independent poor prognostic marker in colorectal cancer.[29] Suzuki *et al.* identified low TLC and high NLR was associated with inferior survival in the extensive-stage small-cell lung cancer.[30] Luo *et al.* indicated high PLR was an independent prognostic indicator of short OS in patients of early stage non-small cell lung cancer who received SABR.[31] Ye *et al.* reported that both high NLR and PLR were correlated with poor survival in patients of nasopharyngeal carcinoma.[32] A meta-analysis by Yodying *et al.* showed elevated pretreatment NLR and PLR were remarkably associated with unfavorable OS of esophageal cancer.[33] In patients undergoing surgery for esophageal squamous cell cancer, PLR was revealed as an independent prognostic factor; moreover, a significantly different survival rate was found between patients in the high NLR group and low NLR group.[34] These results were similar to our analysis. Likewise, Feng *et al.* suggested that PLR should be superior to NLR as a predictive factor in esophageal squamous cell cancer.[35] In addition, others reported that NLR was regarded as an independent prognostic factor for patients with PSCCE.[36] This is mainly because of different inclusion criteria and a various cutoff value of NLR. In the current study, the patients who underwent surgery preceded by neoadjuvant therapy or only accepted chemoradiotherapy and patients diagnosed with distant metastasis were included in the analysis. Wang and Liu suggested the cutoff value to be 2.97 by the ROC analysis and the area under the curve was 0.702. With the same methods, the cutoff value of this study was calculated as 2.37 and the area under the curve was 0.713. To date, there is no standardized optimal cutoff point of inflammatory biomarkers and further research is therefore required.

The limitations of our retrospective study, include a small sample size and data from a single institution. In addition, other biomarkers of the systemic inflammatory response, for example C-reactive protein, fibrinogens, albumin were not included in the analysis. Therefore, large, prospective, multi-center and randomized controlled trials are required to confirm the results of this study.

Conclusion

In conclusion, our study suggested that pretreatment inflammatory biomarkers containing NLR and PLR are related to the survival of patients with PSCCE. The PLR could be deemed as a valuable independent prognostic factor of PSCCE. PLR can be considered as a supplement in distinguishing higher risk group of PSCCE, predicting treatment outcomes and tailoring treatment based on risk stratification. Future multi-center and large clinical trials should be carried out to determine optimal cutoff values of inflammatory biomarkers, after which the further exploration of the independent prognostic value of these inflammatory biomarkers should be considered.

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Disclosure

The authors declare they have no conflict of interest.

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